

**Remarks**

Claims 1-3, 6, 9-11, 24-26, 31-37 and 39-68 are pending in the current application. Claims 1-3, 6, 9-11, 24-26, 31-36, and 39-49 have been withdrawn from consideration as being directed to a non-elected invention. Claims 37 and 50-55, 61-64, and 66-67 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claims 37, 50-55, 61-64, and 66-67 stand rejected under 35 U.S.C. §103(a) as being unpatentable over United States Patent No. 4,728,575 to Gamble et al. in view of a European Journal of Pharm. Biopharmby Ozer et al. The Examiner also noted a minor typographical error in claim 68. The application has been amended. The claims have been amended. Applicants respectfully submit that none of the amendments add new matter in contravention of 35 U.S.C. §132. Reconsideration is respectfully requested.

First, Applicants affirm the election to prosecute the invention of Group II, claims 37 and 50-68. Claims 1-3, 6, 9-11, 24-26, 31-36, and 39-49 are hereby canceled, without prejudice to their forming the basis for a continuation or divisional application claiming priority to the instant application.

Applicants respectfully note that the instant Office Action correctly notes on page 3, second full paragraph, the election made by the Applicants in accordance with the groupings provided on page 2 thereof to prosecute claims 37 and 50-68. Applicants further note that claims 56-60, 65 and 68 have been mistakenly referred to as 'withdrawn from consideration' by the Office Action Summary sheet and are not discussed under the substantive rejections of the Office Action. Moreover, there is no indication of the status of these claims, whether rejected or allowed. Consideration thereof is respectfully requested.

Claims 37, 50-55, 61-64, and 66-67 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

In claim 37, the Examiner objected to the term 'whereof' as being vague and indefinite. This objection is respectfully obviated. Applicants have amended claim 37 to more particularly point out and distinctly claim the subject matter of the invention.

In claim 50, the Examiner objected to the term 'tissue electrical activity' as being vague and indefinite. This objection is respectfully traversed.

Applicants respectfully submit that the term "tissue electrical activity" is well defined and perfectly understandable to a skilled artisan. The present invention is directed to contrast agents and their use in diagnostic applications. Hence a skilled artisan would have at least some background in physiology. It is well known in this art that certain tissue show electrical activity: muscles for instance are stimulated by signals from nerve cells and this stimulation causes electrical activity in the muscle, which in turn causes contraction. One of the most important muscles is the heart and its electrical activity is recorded by electromyography. Brain tissue for instance shows electric activity, which can be monitored and recorded by an electroencephalogram. Abnormal electrical activities recorded by one of these methods help the physician to determine disease states in the corresponding tissue. In view of the understanding of those of ordinary skill in the art, Applicants respectfully submit that the term 'tissue electrical activity' is therefore neither vague nor indefinite. Reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner also noted a minor typographical error in claim 68. The error has been obviated by amendment.

Claims 37, 50-55, 61-64, and 66-67 stand rejected under 35 U.S.C. §103(a) as being unpatentable over United States Patent No. 4,728,575 to Gamble et al. in view of a European Journal of Pharm. Biopharmby Ozer et al. This rejection is respectfully traversed.

Applicants respectfully submit that the Examiner has not met the three basic criteria explicated in the Manual of Patent Examining Procedure ("MPEP") that must be met to establish a *prima facie case* of obviousness. The three basic criteria are: "First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references where combined) must teach or suggest all claim limitations." MPEP §2142.

Further, it is well settled that references are not properly combinable when such combination would destroy that on which the invention of one of the references is based. *Ex parte Hartmann*, 186 USPQ 366 (PTO Bd App 1974).

Gamble describes phospholipids vessels (micelles) which enclose paramagnetic material, e.g. paramagnetic chelate complexes and which are used as contrast agents in MR imaging. The phospholipids vesicles comprise phospholipids like DSPC, DPPC, DMPC and/or cholesterol. However, Gamble is concerned with providing a formulation of micelles and paramagnetic material that simultaneously maximizes micelle stability while permitting adequate rate of water exchange across the membrane (col. 2, l. 23-26). As Gamble explains, "only if water exchanges sufficiently rapid across the bilayer [of a vesicle or micelle] is the relaxation rate of the bulk water enhanced" (col. 2, l. 15-17), i.e. Gamble works the whole paramagnetic micelle as a contrast agent in MR imaging! Gamble does not contain any motivation to modify the micelles in such a way that they respond to a physiological parameter like for instance temperature or pH. Such a modification is neither explicitly nor implicitly mentioned in the disclosure of Gamble.

Ozer et al., meanwhile, describe temperature and pH-sensitive liposomes used in drug delivery. Ozer is completely silent about contrast agents or diagnostic agents encapsulated in such liposomes. Moreover, in order to achieve successful drug delivery, the liposomes have to release their content, e.g. the membrane of the liposomes must be destroyed. Additionally,

Ozer contains no motivation or suggestion to modify the temperature and pH-sensitive liposomes by encapsulating contrast agents instead of drugs.

Neither Gamble nor Ozer, separately or in combination, contain any motivation or suggestion to modify the teachings therein according to the present invention. Gamble is related to MRI contrast agents and Ozer is related to therapeutic drug delivery. Hence the person skilled in the art would not have been motivated to modify and combine the teachings of these references as the competing requirements for a successful drug delivery and for a compound to efficiently work as an MR imaging contrast agent are completely different.

Applicants further submit that the Examiner's comment that one of skill in the art, without the teachings of Ozer et al. would be motivated to produce a liposome that is temperature sensitive, just because lipids are known in the art to change conformation based on temperature, does not establish a *prima facie* case of obviousness. Lipids have many different properties, hence a person skilled in the art had many different possibilities to modify the paramagnetic micelles of Gamble without resulting in temperature or pH-sensitive micelles. It is well settled that "Obvious to try" one of many possibilities or approaches does not establish *prima facie* obviousness (*In re Goodwin*).

Furthermore, as water exchange across the liposome membrane is not sufficient for drug delivery purposes, Applicants respectfully submit that any modification of Ozer to thereby prevent the liposome membrane from being destroyed would be against the implicit teaching of Ozer. As the Examiner's combination of Ozer with Gamble would destroy the invention of Ozer, i.e. prevent drug delivery, Applicants submit that such a combination is impermissible.

Therefore, as neither Gamble nor Ozer disclose, teach, or suggest their modification so as to provide the present invention, and as such a combination would destroy the invention of Ozer, Applicants respectfully submit that the Examiner has failed to meet the burden for establishing a *prima facie* case of obviousness. As a result, Applicants respectfully submit that the present invention, including claims 37 and 50-68 are patentably distinct over the prior art. Reconsideration and withdrawal of the rejection are respectfully requested.

In view of the amendments and remarks herein, Applicants believe that each ground for rejection or objection made in the instant application has been successfully overcome or obviated, and that all the pending claims, including claims 37 and 50-68 are in condition for allowance. Favorable action thereon is respectfully requested.

The Examiner is invited to telephone the undersigned in order to resolve any issues that might arise and to promote the efficient examination of the current application.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'R. F. Chisholm', written over a horizontal line.

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